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Clinical Course of Breast Cancer Patients with Isolated Sternal and Full-Thickness Chest Wall Recurrences Treated With and Without Radical Surgery

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ABSTRACT

Background. The role and outcome of radical surgery in contemporary multidisciplinary management of breast cancer patients presenting with isolated sternal or full-thickness chest wall (SCW) recurrence are undefined compared with patients treated without surgery.

Methods. Detailed analyses of all patients with isolated SCW recurrence treated from 1992 to 2011 at a large cancer institution were performed. Univariate and multivariate comparisons of clinicopathologic and treatment characteristics were analyzed. Overall and progression-free survival were compared using the Kaplan–Meier method.

Results. Seventy-six patients were identified, 44 treated surgically and 32 nonsurgically. Overall survival at 5 years was not statistically different between patients who underwent surgery and those who did not (30.6 and 49.6 %, respectively; $P = 0.52$) although patients selected for surgery presented with more advanced and biologically aggressive disease. Surgically treated patients were more likely to have triple-negative breast cancer at recurrence (52 vs. 17 %; $P = 0.006$). Among surgical patients, 95 % received preoperative systemic therapy. Clinical response with systemic therapy was significantly different, with surgically treated patients more likely to have responsive or stable disease (54 vs. 25 %, $P = 0.04$). Complications related to radical surgical resection occurred in 25 % of patients. For hormone receptor–positive recurrence, 5-year progression-free survival was significantly higher among surgical patients (46.3 vs. 14.5 %; $P = 0.01$).

Conclusions. Among patients with isolated SCW recurrence, hormone receptor-positive recurrence is associated with improved survival. Systemic therapy should be the initial treatment, and clinical response can be used to help select patients who may benefit from radical resection.

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Isolated sternal and/or full-thickness chest wall (SCW) recurrences represent a management challenge. There are no strong data regarding how best to manage these recurrences. Breast cancer patients often receive radiotherapy as a component of their initial treatment, which may limit or preclude use of radiotherapy as a definitive or adjuvant therapy for isolated locoregional recurrence.[1] Operative intervention can be complex, requiring multidisciplinary surgical teams with an appreciable rate of perioperative morbidity.[2–5] There are few centers with broad experience in the often complicated management of these rare recurrences.

Several questions about the care of patients presenting with isolated SCW breast cancer recurrence remain unanswered. With varying opinions regarding the utility of

surgical intervention, its role in the management of these patients remains unclear.[3,6,7] Assuming surgery represents an effective therapeutic modality, it is also important to understand the patient subgroups for which surgery can and should be considered. Currently, no management algorithm has been described to direct providers in the management of patients who develop SCW recurrence. As such, the purpose of this work was to obtain a better understanding of the clinical course of SCW recurrence when managed surgically and nonsurgically, define factors that may predict improved clinical outcome, and to describe potential management strategies for such recurrences.

PATIENTS AND METHODS

The prospectively maintained databases of the departments of surgical oncology, thoracic and cardiovascular surgery, plastic surgery and the breast cancer management system were utilized to identify all patients treated for isolated SCW recurrence at the University of Texas MD Anderson Cancer Center from 1992 to 2011. SCW recurrence was defined as a recurrence involving the sternum and/or ribs and/or intercostal muscles with or without skin involvement. Patients with chest wall recurrence limited to the skin and/or underlying muscle, patients who had distant metastases at initial diagnosis, patients who had distant metastases at the time of SCW recurrence, and patients with angiosarcoma were excluded.

Upon diagnosis of recurrent breast cancer, all patients underwent an assessment for metastatic disease, which involved but was not limited to some combination of plain-film X-ray studies, computed tomography of the chest and abdomen, bone scan, positron emission tomography, and combined positron emission tomography–computed tomography. Prespecified demographic and clinicopathologic variables were collected and analyzed. The institutional review board of the MD Anderson Cancer Center approved this study.

Descriptive statistics were utilized in the tabulation of the data. Patients were stratified into two groups: those managed with radical resection ($n = 44$) and those managed nonoperatively ($n = 32$). The primary outcome was overall survival (OS), defined as time from the date of diagnosis of SCW recurrence to the date of last follow-up or death from any cause. Secondary endpoints included perioperative morbidity and progression-free survival (PFS), defined as time from the date of diagnosis of SCW recurrence to the date of last follow-up, development of additional locoregional recurrence, development of distant metastases, or death. OS and PFS were estimated using the Kaplan-Meier method and differences were assessed using the log-rank test.

In an exploratory analysis, variables found to be statistically significant on univariate analysis were used to perform a multivariate analysis using a Cox proportional hazard model to identify potential risk factors associated with survival. All reported P values are two-sided, and P values <0.05 were considered statistically significant. All analyses were performed by Stata/IC (release 11.1; Stata-Corp, College Station, TX, USA).

RESULTS

Seventy-six patients with breast cancer and isolated SCW recurrence after definitive primary therapy were treated at our institution from 1992 to 2011. Overall median follow-up time among surviving patients was 3.6 years (range 0.4–16.9 years). Demographic, pathologic, and clinical characteristics are summarized in Table 1. Median age at initial breast cancer diagnosis was 44.5 years. Fifty-six of the 76 patients (73.7 %) had stage I or II breast cancer at the time of initial diagnosis, and 69 patients (91 %) had infiltrating ductal carcinoma. Thirty-four patients (45 %) were treated initially with mastectomy plus radiotherapy, and 22 patients (29 %) were treated with mastectomy alone; whereas, 17 patients (22 %) were treated initially with breast-conserving surgery plus radiotherapy, and 3 patients (4 %) with breast-conserving surgery alone.

Just over half the patients (54 %) had SCW recurrences that were positive for estrogen receptor (ER); 23 % of patients for whom HER2 status was known had HER2-positive recurrences. Twenty-five patients (40 %) had a triple-negative recurrence. The median time from initial cancer diagnosis to SCW recurrence was 2.7 years (range 0.03–17.4 years). Median times to additional local-regional recurrence ($n = 25$, 32.8 %) and development of distant site metastases ($n = 47$, 61.8 %) after SCW recurrence were 1.34 years (range 0.4–9.7 years) and 1.83 years (range 0.3–7.2 years), respectively.

Comparison of Patients with and Without Radical Resection

Forty-four patients (58 %) underwent surgical resection. The majority (70 %) who underwent resection were aged 50 years or younger. Patients in the surgery group were more likely than those in the nonsurgical group to have early recurrence after definitive management of the initial breast cancer (52 % of the surgery group had recurrence diagnosed within 2 years; 75 % of the nonsurgical group had recurrence diagnosed after 2 years; $P = 0.017$). Patients in the surgery group were significantly more likely to present with a finding on physical examination at the

TABLE 1 Demographic, pathologic, and clinical characteristics of patients who developed sternal/chest wall recurrence (n = 76)

Characteristic	Overall no. of patients	Surgery (n = 44)	No surgery (n = 32)	P value
Initial disease				
Age				
Median (range), years	44.5 (27–67)	45.5 (31–65)	44.5 (27–67)	0.91
≤50 years	53	31 (70.4)	22 (68.7)	
>50 years	23	13 (29.6)	10 (31.3)	0.87
Race/ethnicity				0.11
White	62	38 (86.4)	24 (75.0)	
African-American	6	3 (6.8)	3 (9.4)	
Hispanic	6	1 (2.3)	5 (15.6)	
Asian	2	2 (4.5)	0 (0)	
Tumor histology				0.67
Infiltrating ductal carcinoma	69	40 (90.9)	29 (90.6)	
Mixed invasive tumor	3	1 (2.3)	2 (6.3)	
Ductal carcinoma-in situ	3	2 (4.5)	1 (3.1)	
Lobular carcinoma-in situ	1	1 (2.3)	0 (0)	
Stage at diagnosis				0.41
0	3	2 (4.6)	1 (3.1)	
I	21	9 (20.9)	12 (37.5)	
II	35	21 (48.8)	14 (43.7)	
III	16	11 (25.6)	5 (15.6)	
Unknown	1	1	0	
Definitive surgery and radiotherapy				0.01
Breast-conserving surgery plus radiotherapy	17	9 (20.4)	8 (25.0)	
Breast-conserving surgery alone	3	1 (2.3)	2 (6.2)	
Mastectomy plus radiotherapy	22	19 (43.2)	3 (9.4)	
Mastectomy alone	34	15 (34.1)	19 (59.4)	
Endocrine therapy				0.11
Yes	37	18 (40.9)	19 (59.4)	
No	39	26 (59.1)	13 (40.6)	
Chemotherapy				0.19
Yes	58	36 (81.8)	22 (68.7)	
No	18	8 (18.2)	10 (31.2)	
Trastuzumab				0.30
Yes	5	4 (9.1)	1 (3.1)	
No	71	40 (90.9)	31 (96.9)	
Neoadjuvant therapy				0.41
Yes	10	7 (15.9)	3 (9.4)	
No	66	37 (84.1)	29 (90.6)	
Response to neoadjuvant therapy				
Pathologic complete	0	0 (0)	0 (0)	
Not pathologic complete	10	7 (100.0)	3 (100.0)	
Recurrence				
Time to recurrence				0.02
≤2 years	31	23 (52.3)	8 (25.0)	
>2 years	45	21 (47.7)	24 (75.0)	
Findings at physical examination at time of recurrence				0.006

TABLE 1 continued

Characteristic	Overall no. of patients	Surgery (n = 44)	No surgery (n = 32)	P value
Mass with or without ulceration	33	25 (56.8)	8 (25.0)	
Radiographic finding only	43	19 (43.2)	24 (75.0)	
Concurrent breast or skin recurrence				0.16
No	58	31 (70.4)	27 (84.4)	
Yes	18	13 (29.6)	5 (15.6)	
Estrogen receptor status				0.07
Positive	39	19 (45.2)	20 (66.7)	
Negative	33	23 (54.8)	10 (33.3)	
Unknown	4	2	2	
Progesterone receptor status				0.07
Positive	20	9 (21.4)	11 (42.3)	
Negative	48	33 (78.6)	15 (57.7)	
Unknown	8	2	6	
HER2 status[a]				0.008
Positive	16	5 (11.9)	11 (39.3)	
Negative	54	37 (88.1)	17 (60.7)	
Unknown	6	2	4	
Triple-negative breast cancer				0.006
Yes	25	21 (52.5)	4 (17.4)	
No	38	19 (47.5)	19 (82.6)	
Unknown	13	4	9	
Nodal involvement				0.15
Yes	31	21 (47.7)	10 (31.3)	
No	45	23 (52.3)	22 (68.7)	
Location of recurrence				0.002
Sternal only	34	13 (29.5)	21 (65.6)	
Sternal and/or chest wall/ribs	42	33 31 (70.5)	11 (34.4)	
Systemic therapy				0.22
Yes	74	42 (95.5)	32 (100)	
No	2	2 (4.5)	0 (0)	
Endocrine therapy				0.23
Yes	17	12 (27.3)	5 (15.6)	
No	59	32 (72.7)	27 (84.4)	
Radiotherapy[b]				0.02
Yes	41	30 (68.2)	29 (90.6)	
No	35	14 (31.8)	3 (9.4)	
Response to systemic therapy				0.04
Complete or partial	14	10 (24.4)	4 (12.5)	
Stable disease	16	12 (29.3)	4 (12.5)	
Progression	43	19 (46.3)	24 (75.0)	
Unknown	3	3	0	
Timing of systemic therapy among surgical patients[c]				
Preoperative	–	42 (95.5)	–	
Postoperative	–	22 (50.0)	–	
Both	–	16 (36.4)	–	
None	–	2 (4.5)	–	

TABLE 1 continued

Characteristic	Overall no. of patients	Surgery (n = 44)	No surgery (n = 32)	P value
Timing of postoperative chemotherapy among surgical patients				
Within 8 weeks	–	6 (13.6)	–	
After 8 weeks	–	10 (22.7)	–	
None	–	25 (56.8)	–	
Unknown	–	3 (6.8)	–	
Additional locoregional disease after SCW recurrence				0.45
Yes	25	16 (36.4)	9 (28.1)	
No	51	28 (63.6)	23 (71.9)	
Time to additional locoregional disease after SCW recurrence				0.82
Median (range), years	1.34 (0.4–9.7)	1.5 (0.4–5.1)	2.4 (0.5–9.7)	
Additional distant metastasis after SCW recurrence				0.01
Yes	47	22 (50.0)	25 (78.1)	
No	29	22 (50.0)	7 (21.9)	
Time to development of distant metastases after SCW recurrence				0.42
Median (range), years	1.83 (0.3–7.8)	1.7 (0.5–7.8)	1.8 (0.3–7.2)	

SCW sternal or full-thickness chest wall

[a] Positive was defined as 3+ on immunohistochemistry or positive by fluorescence in situ hybridization

[b] Twelve patients received radiotherapy before resection, and 18 patients received radiotherapy after resection

[c] Includes endocrine therapy

time of recurrence (57 vs. 25 %; $P = 0.006$), whereas patients in the nonsurgical group were significantly more likely to present with only a radiographic finding (75 vs. 43 %; $P = 0.006$). Patients in the surgery group were significantly more likely to have a triple-negative recurrence (52 vs. 17 %; $P = 0.006$). Patients in the nonsurgical group were more likely to have recurrence isolated to the sternum (66 vs. 30 %; $P = 0.002$). There was no difference between the surgical and nonsurgical groups in terms of additional locoregional recurrence after SCW recurrence.

The vast majority of patients in both the surgical (93 %) and nonsurgical (91 %) groups underwent multimodality treatment (92 % overall cohort). Nearly all patients in the surgical group (95 %) and 100 % of patients in the nonsurgical group received some form of systemic therapy for their SCW recurrence. In the surgery group, all patients who received chemotherapy received it preoperatively. There were only three (6.8 %) surgeries performed specifically for palliative indications in the absence of other known distant-metastases, two for ulceration/nonhealing full-thickness chest wall wounds and one for intractable severe pain. The majority (57 %) of patients in the surgery group received no additional postoperative chemotherapy. Clinical response to systemic therapy was significantly different between the groups with patients undergoing surgery more likely to have responsive or stable disease (54 vs. 25 %, $P = 0.04$). Radiotherapy for treatment of recurrence was significantly more common in the nonsurgical group (91 vs. 68 %, $P = 0.02$). Overall, ~41 % of patients ($n = 16$) who had initial radiotherapy for their primary breast cancer had reirradiation for their SCW recurrence, most of which ($n = 11$) were in the nonsurgical group.

Details of Surgical Resection and Reconstruction

Among the 44 patients who underwent resection of their isolated SCW recurrence, 11 underwent resection of sternum alone, 11 underwent resection of ribs/chest wall alone, 11 underwent resection of sternum and ribs/chest wall, and 11 underwent resection of sternum, ribs/chest wall, and other structures or organs in which tumor involvement was identified during surgery but not during the preoperative assessment. These other structures or organs included the thymus ($n = 2$), diaphragm ($n = 1$), lung ($n = 5$), clavicular heads ($n = 2$), and pericardium ($n = 1$). For all of these other structures or organs, pathologic evaluation confirmed disease involvement. Soft tissue reconstruction was necessary in 42 patients (95 %) and was performed with pectoralis major muscle in 18 patients, a free rectus abdominis flap in 9 patients, and a combination of multiple soft tissue reconstruction techniques in the remaining 15 patients. Bone reconstruction was necessary in 28 patients (64 %) and was accomplished with nonabsorbable flexible mesh, nonabsorbable rigid mesh, and/or biologic mesh.

There were no postoperative deaths. Complications occurred in 11 patients (25 %), some of whom experienced multiple complications. The complications were as follows: local infection ($n = 8$), partial reconstructive flap necrosis ($n = 4$), respiratory ($n = 3$), cardiovascular ($n = 2$), full-thickness reconstructive flap necrosis ($n = 1$), need for prosthetic material to be removed ($n = 1$), and chyle leak ($n = 1$).

Overall and Disease-Free Survival

For the entire cohort, the 5-year OS rate was 39.5 % and the 5-year PFS rate was 22.7 %. Several variables were analyzed in an attempt to identify factors associated with OS and/or PFS. No significant difference was noted in 5-year OS rate between patients who underwent surgery and those who did not (30.6 and 49.6 %, respectively; $P = 0.52$; Fig. 1). Similarly, PFS at 5 years was not significantly different between patients who underwent surgery and those who did not (30.2 and 14.8 %, respectively; $P = 0.19$; Fig. 1). Compared to patients with ER-negative recurrences, patients with ER-positive recurrences had a higher 5-year OS rate (48.4 vs. 26.8 %; $P = 0.001$) and a higher 5-year PFS rate (34.7 vs. 9.5 %; $P = 0.004$). Consistent with this, patients with triple-negative breast cancer had significantly lower OS (23.9 vs. 46.0 %, $P = 0.02$) and PFS (12.6 vs. 29.3 %, $P = 0.04$.) On multivariate analysis, there were no clear predictors of OS, but ER-negative recurrence was significantly associated with worse PFS (hazard ratio 1.75; 95 % CI 1.01–3.05; $P = 0.04$).

Table 2 shows 5-year OS and PFS for patients in the surgical and nonsurgical groups stratified by various clinical and pathologic factors. None of the factors was associated with a difference in 5-year OS comparing patients in the surgical and nonsurgical groups. The only significant finding was an association between hormone receptor-positive disease and PFS. Among patients with hormone receptor-positive disease, 5-year PFS was 46.3 % in the surgical group compared with 14.5 % in the nonsurgical group ($P = 0.01$; Fig. 2). Among patients who underwent surgery, increased magnitude of resection appeared to be associated with lower rates of both 5-year OS (sternum only, 47.7 %; ribs/chest wall only, 36.8 %; sternum and ribs/chest wall, 29.6 %; sternum, ribs/chest wall, and other organs/structures, 11.4 %) and PFS (sternum only, 50.9 %; ribs/chest wall only, 31.2 %; sternum and ribs/chest wall, 28.4 %; sternum, ribs/chest wall, and other organs/structures, 13.6 %).

DISCUSSION

Isolated SCW recurrence continues to be an issue for breast cancer patients. To our knowledge, this study represents the largest contemporary experience regarding patients with apparent isolated SCW recurrences. Importantly, we have demonstrated that multidisciplinary treatment of isolated SCW recurrences can result in 5-year OS rates of ~ 40 %, with improved outcomes observed in patients with hormone receptor-positive recurrences. We found no survival benefit for patients undergoing surgical resection and in fact, as the complexity of the surgical resection and reconstruction increased, the therapeutic benefit appears to decrease, suggesting surgical resection should only be performed in carefully selected patients.

In the overall cohort, we found 5-year OS and PFS of 39.5 % (surgical group, 30.6 %; nonsurgical group, 49.6 %) and 22.7 % (surgical group, 30.2 %; nonsurgical

FIG. 1 Five-year OS (**a**) and PFS (**b**) among patients with SCW recurrence surgically and nonsurgically managed
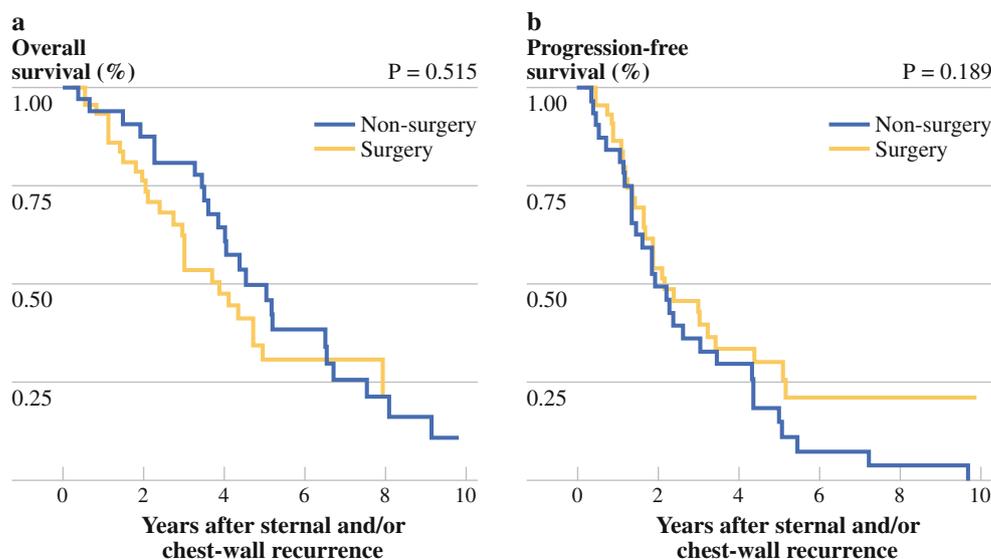
TABLE 2 Five-year overall and progression-free survival rates among patients with and without radical resection of sternal/chest wall recurrence

Characteristic	Overall survival (%)			Progression-free survival (%)		
	Surgery	No surgery	P value	Surgery	No surgery	P value
All patients	30.6	49.6	0.52	30.2	14.8	0.19
Estrogen receptor status						
Positive	45.0	50.5	0.51	46.3	25.5	0.07
Negative	16.5	50.0	0.40	13.9	0	0.71
Hormone receptor status						
Triple negative	18.1	50.0	0.69	15.2	0	0.37
Hormone receptor positive	45.0	47.0	0.25	46.3	14.5	0.01
Sternal-only recurrence	37.1	53.0	0.79	45.0	18.1	0.89
Disease-free interval[a]						
≤2 years	28.5	37.5	0.59	37.6	12.5	0.11
>2 years	30.0	53.1	0.08	24.2	15.2	0.67
Nodal involvement at recurrence						
Yes	14.8	25.0	0.75	9.4	0	0.84
No	44.5	60.1	0.97	43.7	19.8	0.08
Stage 0–II disease at initial diagnosis	26.1	43.1	0.34	24.4	18.0	0.63
Findings at physical examination at recurrence[b]						
Yes	32.3	37.5	0.62	30.1	12.5	0.20
No	25.9	53.7	0.17	31.9	15.6	0.62

[a] From initial cancer diagnosis to diagnosis of sternal or full-thickness chest wall recurrence

[b] Mass with or without ulceration

FIG. 2 Five-year OS (**a**) and PFS (**b**) among patients with hormone receptor-positive SCW recurrence surgically and nonsurgically managed
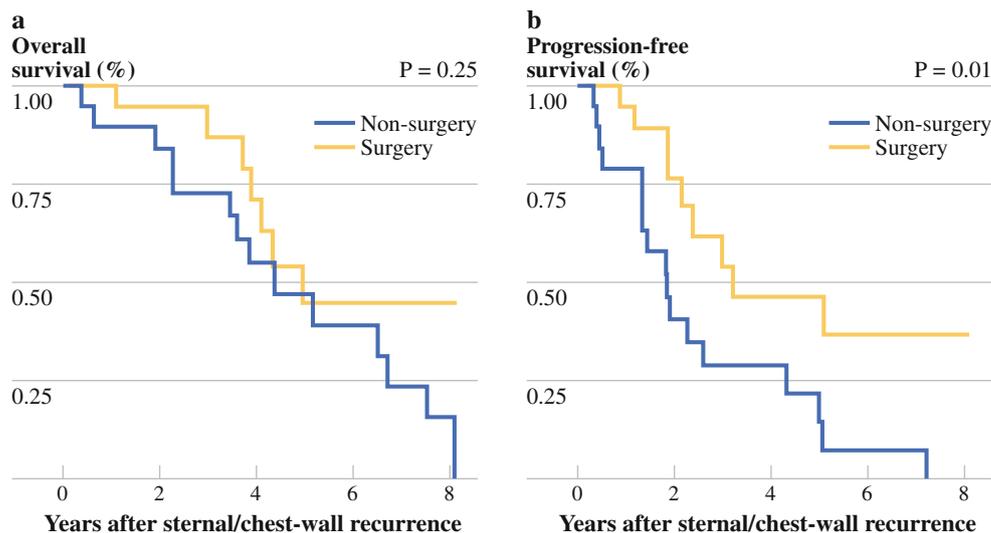
group, 14.8 %), respectively, consistent with the 18–71 and 13–67 % (respectively) reported by other groups over the past 40–50 years.[3–6,8,9] It is important to note that many prior series were composed of mixed groups of patients, some of whom had distant metastatic disease at the time of presentation with SCW recurrence. By comparison, our cohort was limited to patients without other distant metastases.

Our study is similar in design to an early report on this topic published by Snyder et al.[9] The authors reported results from a cohort that also included 76 patients with breast cancer chest wall recurrences divided into two subgroups: 24 who underwent full-thickness chest wall resection (including resection of muscle, ribs, and portions of sternum as necessary) and 52 treated with less radical surgery, radiation, and/or other palliative measures. The

5-year survival in surgically treated patients was 30 %, similar to the survival rate in surgically treated patients in the present cohort. In 1975, Shah and Urban[8] also reported a 5-year survival of 30 % for patients who underwent chest wall resection for recurrent breast carcinoma. Although direct comparison to historical cohorts from several decades ago is subject to significant bias, it is worth noting that even with advances in surgical and reconstructive techniques, as well as the advent of and improvement in adjuvant therapies, there was no difference in survival between women in the earlier series and those in our series who underwent surgical resection of SCW breast cancer recurrence. In contrast, 5-year survival among nonsurgically managed patients in our contemporary cohort was dramatically better compared to patients in the Snyder et al. study treated without radical resection: nearly 50 versus 13 %—a difference likely due to improved imaging/ detection and available therapies.

One key advance in breast cancer management is improved understanding of prognosis as it relates to biologic subtype and the development of targeted therapies for some breast cancer subtypes. We found that hormone receptor status plays an important prognostic role, a finding demonstrated in at least one prior study evaluating SCW recurrences.[4] Patients with surgically resected, hormone receptor-positive disease had a better 5-year OS rate than patients with surgically resected, triple-negative breast cancer (45 vs. 18 %).

Another notable finding of our study was the fact that ~79 % of the women in our cohort initially presented with stage 0, I, or II disease. This finding is similar to one previously reported by Santillan et al.[4] Only recently has the molecular basis of breast cancer begun to be uncovered.[10] In this context, our finding of earlier-stage disease at initial presentation may signal that the underlying disease biology is as important, if not more important, than stage in terms of predicting recurrence and long-term outcome. Alternatively, our finding may simply be explained by selection bias within our cohort as patients with distant metastases (other than isolated SCW recurrence), who might be more likely to have had stage III breast cancer at initial presentation, were excluded from this analysis.

Although this investigation is the largest contemporary study and contributes important information regarding the management and natural history of patients treated with and without radical resection for SCW recurrence, there are also limitations to consider when interpreting these results. Although our study provides valuable information regarding the clinical course of both surgical and nonsurgical contemporary approaches to the management of breast cancer recurrence of the sternum and/or chest wall, our data do not allow us to definitively define what constitutes appropriate management for such patients. Patients treated with medical therapy compared with radical surgery in this retrospective analysis were older, had earlier less extensive and biologically less aggressive disease.

In conclusion, on the basis of the findings in this study the following algorithm for the multidisciplinary management of SCW breast cancer recurrence was generated. Patients should be initiated on systemic therapy as first-line management. Surgery may then be considered for patients with hormone receptor-positive disease, patients with recurrence that presents a potential quality-of-life issue, or patients with responsive or persistent, nonprogressive disease in the absence of other distant disease. In the absence of clear data to allow firm management recommendations, patients with isolated SCW recurrence are most likely best treated at centers with multidisciplinary teams experienced in the management of complex breast cancer recurrence and teams that can perform complicated resections/reconstructions and manage the morbidity of such interventions.

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